

# PATENT SPECIFICATION

NO DRAWINGS

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## COMPLETE SPECIFICATION

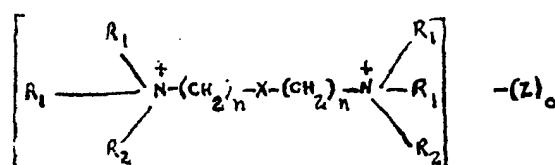
### Poly-Onium Neuromuscular Blocking Agents

We, NATIONAL RESEARCH DEVELOPMENT CORPORATION, a British Corporation, established by Statute, of 1 Tilney Street, London, W.1, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to neuromuscular

blocking agents and its objects is to provide by synthesis certain poly-onium compounds which have been tested on animals and are found to have properties by virtue of which they are suitable as such agents, acting in some respects like tubocurarine and decamethonium.

The invention comprises a poly-onium compound of the general formula



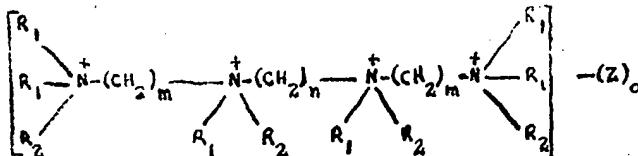
in which X represents  $\overset{+}{N}$ ,  $\overset{+}{S}$  or  $\overset{+}{S}$   
 $\wedge$   
 $R_1 \quad R_2 \quad R_1 \quad R_2$

n is an integer not less than 4  
Z is a non-toxic anion

o is equal to the number of onium groups in the compound divided by the valency of the anion.

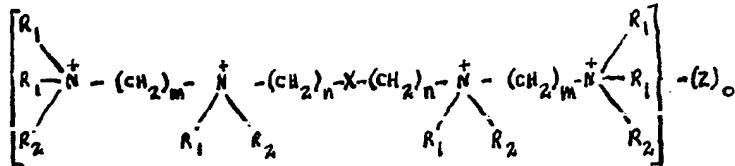
20 R<sub>1</sub>, R<sub>2</sub> represent alkyl groups and are the same or different

The invention also comprises a poly-onium compound of the general formula



30 in which R<sub>1</sub>, R<sub>2</sub>, n, Z and o are as hereinbefore defined and m is an integer not less than 4.

The invention also comprises a poly-onium compound of the general formula



in which  $R_1$ ,  $R_2$ ,  $Z$ ,  $X$ ,  $n$ ,  $m$  and  $o$  are as hereinbefore defined.

5 The anion is preferably iodine but this element as such is not critical to the activity of each compound as a blocking agent, and therefore there may be substituted any pharmaceutically equivalent anion, for example the bromide, the chloride, or the tartrate. The 10 alkyl radical may be ethyl (Et) but it may instead be methyl (Me) or it might be propyl, isopropyl, normal butyl, secondary butyl, tertiary butyl or amyl.

15 Preferably  $R_1$  and  $R_2$  represent alkyl groups containing from 1 to 4 carbon atoms.

15 Preferably also  $m$  and  $n$  represent integers from 5 to 10.

20 The invention also comprises the following novel intermediate compounds formed in the preparation of the poly-onium compounds according to the invention:

Bis-5-diethylaminopentyl sulphide.

Bis-(6-diethylaminohexyl) ethylamine.

Bis-(10-diethylaminodecyl) ethylamine.

25 1: 20 - Bis - (diethylamino) - 7: 14 - diethyl - 7: 14-diazaeicosane.

1: 32 - Bis - (diethylamino) - 1: 1: 22 - diethyl - 11: 22 - diazadotriaccontane.

30 Bis - (13 - diethylamino - 7 - ethyl - 7 - azatridecyl) sulphide.

Bis-8-diethylaminoctyl sulphide.

Bis-(8-diethylaminoctyl) ethylamine.

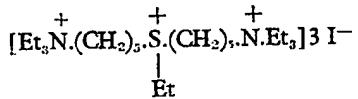
1: 28 - Bis - (diethylamino) - 11: 18 - diethyl - 11: 18 - diazaoctacosane.

35 1: 24 - Bis - (diethylamino) - 7: 18 - diethyl - 7: 18 - diazatetracosane.

By way of illustration specific compounds representative of the series according to the foregoing general formulae and methods of preparing such compounds will now be described.

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#### EXAMPLE 1.



45 6 - Ethyl - 6 - thoniaundecylenebis (triethylammonium) triiodide was prepared from 5-hydroxypentyl diethylamine (Synerholm, *J. Amer. Chem. Soc.* 1947, 69, 2581) through the intermediate bis-5-diethylaminopentyl sulphide as follows:

50 Bis-5-diethylaminopentyl Sulphide. Excess thionyl chloride (9 ml.) in benzene (20 ml.)

was slowly added to a stirred solution of 5-hydroxypentyl diethylamine (14.3 g.) in benzene (100 ml.). The yellow crystalline mass obtained on removal of the solvent and excess reagent was dissolved in water (20 ml.), the solution cooled to 0° C, and basified with sodium hydroxide solution (30 ml.; 20%).

Extraction with ether, drying ( $\text{Na}_2\text{SO}_4$ ), and evaporation of the solvent gave crude 5-chloropentyl diethylamine (15.9 g.). The latter in ethanol (8 ml.) was slowly added to a hot solution of anhydrous sodium sulphide (4.4 g.) in water (5 ml.) and ethanol (16 ml.), and the mixture refluxed for 3 hours with continuous stirring.

The residual liquid, after removal of the solvent at 100° C was poured into brine (50 ml.), and extracted with ether. The ethereal extracts were dried ( $\text{Na}_2\text{SO}_4$ ), evaporated, and the residue distilled to yield

bis - 5 - diethylaminopentyl sulphide as a pale yellow oil (3.55 g., 25%), b.pt. 200-205°

C/1.2 mm.  $n_{D}^{20.5}$  1.4707. Found: equiv. (titration) 157.3  $\text{C}_{16}\text{H}_{34}\text{N}_2\text{S}$  requires equivalent 158.3. Bis - 5 - diethylaminopentyl sulphide dihydrochloride (from ethanol-ether),

m.pt. 155-156° C. Found: C, 55.8; H, 10.9%.  $\text{C}_{18}\text{H}_{34}\text{N}_2\text{S}\text{Cl}_2$  requires C, 55.5; H, 10.9%)

6 - Ethyl 6 - thoniaundecylenebis (triethylammonium) triiodide. Bis - 5 - diethylaminopentyl sulphide (0.85 g.) was refluxed with excess ethyl iodide (4 ml.) for not less than 40 minutes.

Removal of excess reagent under reduced pressure, and recrystallisation of the product from ethanol gave 6 - ethyl - 6 - thoniaundecylenebis (triethylammonium) triiodide (1.1 g.) m.pt. 136.5-137.5° C. Found. I, 48.3; N, 3.5%  $\text{C}_{24}\text{H}_{55}\text{N}_2\text{S}\text{I}_3$  requires I, 48.5; N, 3.6%.

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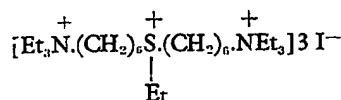
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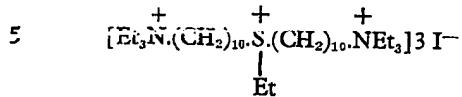
#### EXAMPLE 2.



7 - Ethyl - 7 - thoniaundecylenebis (triethylammonium) triiodide was prepared from bis-6-diethylaminohexyl sulphide (Edwards and Stenlake, *J. Pharm. Pharmacol.*, 1955, 7, 852) (1.64 g.) by refluxing with ethyl iodide (3 ml.) for 25 mins. Removal of excess reagent under reduced pressure and recrystallisation of the product from ethanol gave almost colourless crystals (2.95 g., 76.3%) of 7-ethyl-7-thonia-

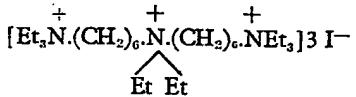
tridecylenebis (triethylammonium) triiodide, m.pt. 142-143° C. Found: N, 3.7; I, 46.6%  $C_{26}H_{48}N_2Si_3$  requires N, 3.5; I, 46.9%.

## EXAMPLE 3.



11 - Ethyl - 11 - thioniaheneicosylenebis (triethylammonium) triiodide was prepared from bis - 10 - diethylaminodecyl sulphide (1.1g.) (Edwards and Stenlake, *J. Pharm. Pharmacol.*, 1955, 7, 852) by refluxing with ethyl iodide (2 ml.) and ethanol (1 ml.) for 45 minutes. Evaporation to dryness under reduced pressure yielded 11 - ethyl - 11 - thioniaheneicosylenebis (triethylammonium) triiodide (0.6 g., 27%).  
 10 m.p. 123.5-124° C. (from acetone-ether). Found: N, 3.0; H, 41.2%  $C_{34}H_{76}N_2Si_3$  requires, N, 3.0; I, 41.2%.

## EXAMPLE 4.



20 7:7 - Diethyl - 7 - azoniatridecylenebis (triethylammonium) triiodide was prepared from 6 - hydroxyhexyldiethylamine (Work, *J. Chem. Soc.*, 1942, 426; Edwards and Stenlake, *J. Pharm. Pharmacol.*, 1955, 7, 852), through the intermediates 6 - bromohexyldiethylamine, 6 - diethylaminohexyldiethylamine and bis(6-diethylaminohexyl)ethylamine as follows:  
 6 - Bromohexyldiethylamine. 6-Hydroxyhexyldiethylamine (35.2 g.) was refluxed with 48% hydrobromic acid (95 ml.) and concentrated sulphuric acid (33 ml.) for 4 hours. The cooled solution, diluted with water (1 L) was basified with sodium carbonate, and extracted with chloroform. Evaporation of the solvent under reduced pressure at 17° C., and filtration of solid matter from the oily residue gave 6-bromohexyldiethylamine as a reddish brown oil containing traces of chloroform, which was used immediately in the next stage.

30 6 - Diethylaminohexyldiethylamine. Crude 6-bromohexyldiethylamine and excess ethylamine (40 ml.) were refluxed for 2 hours. Evaporation of the chloroform and excess ethylamine yielded a damp crystalline residue which was basified and extracted with ether. Evaporation of the ether yielded an oil (24.8 g.) which on distillation gave 6 - diethylaminohexyldiethylamine, b.p. 86-89° C./0.55 mm.  $n_D^{17}$  1.4493, (21.5 g., 53%). *Dihydrochloride* (from ethanol-ether), m.p. 172-173° C. Found: C, 51.8; H, 10.6; Cl, 25.8%.  $C_{12}H_{24}N_2Cl_2$  requires C, 52.7; H, 11.1; Cl, 25.9%.

Bis - (6 - diethylaminohexyl)ethylamine. 6 - Diethylaminohexyldiethylamine (Work, *J. Chem. Soc.*, 1942, 426; Edwards and Stenlake, *J. Pharm. Pharmacol.*, 1955, 7, 852) (6.3 g.) in xylene (20 ml.) for 5 hours. On cooling the reaction mixture was extracted with dilute hydrochloric acid (10%) and the latter basified and extracted with benzene. Evaporation of the solvent and fractional distillation of the residue gave bis - (6 - diethylaminohexyl)ethylamine, as a pale yellow oil, b.p. 165-168° C./0.07 mm,  $n_D^{18}$  1.4610 (2.2 g., 19%). Found: C, 74.7; H, 13.1 per cent.  $C_{22}H_{44}N_3$  requires C, 74.3; H, 13.1 per cent.

7:7 - Diethyl - 7 - azoniatridecylenebis (triethylammonium) triiodide. Bis - (6 - diethylaminohexyl)ethylamine (0.57 g.) was refluxed with ethyl iodide (3 ml.) for 15 minutes. Evaporation of excess ethyl iodide yielded 7:7 - Diethyl - 7 - azoniatridecylenebis (triethylammonium) triiodide (1.02 g., 77%), m.p. 261-262° C. (from ethanol). Found: N, 4.95; I, 46.2%.  $C_{28}H_{64}N_2I_3$  requires N, 5.1; I, 46.2%.

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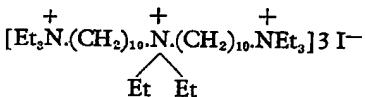
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## EXAMPLE 5.



11:11 - Diethyl - 11 - azoniaheneicosylenebis (triethylammonium) Triiodide was prepared from 10-Hydroxydecyldiethylamine (Schinzel and Benoit, *Bull. Soc. Chim. Fr.*, 1939, [5], 6, 501; Edwards and Stenlake, *J. Pharm. Pharmacol.*, 1955, 7, 852) through the intermediate 10-bromodecylidethylamine, 10-diethylaminodecylethylamine and bis(10-diethylaminodecyl)-ethylamine as follows:

10 - Diethylaminodecylethylamine 10 - from 10-hydroxydecyldiethylamine (20.1 g.) by the method described for 6-bromohexyldiethylamine, and was obtained as a colourless oil, bp. 130° C./0.5 mm,  $n_D^{14}$  1.4714 (21.4 g. 84%). Found: Equiv. (titration) 294.3; Br, 27.25 per cent.  $C_{11}H_{24}NBr$  requires equiv. 292.3; Br, 27.3 per cent.

10 - Diethylaminodecylethylamine 10 - Bromodecylidethylamine (20.9 g.) and excess ethylamine (60ml.) were refluxed for 2 hours. Distillation of the excess ethylamine, addition of water to the residue and extraction with benzene yielded an oily product which on distillation gave 10-diethylaminodecylethylamine b.p. 133-135° C./0.8 mm. (14 g.),  $n_D^{19}$  1.4535, together with bis - (10 - diethylaminodecyl)ethylamine, b.p. 216-217° C./0.75 mm. (0.9 g.). 10 - Diethylaminodecylethylamine Dihydrochloride (from ethanol-ether), m.p. 147-148° C. Found: C, 58.1; H, 11.4; Cl, 20.3 per cent.  $C_{12}H_{24}N_2Cl_2$  requires C, 58.3; H, 11.6; Cl, 21.5 per cent.

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5 *Bis - (10 - diethylaminodecyl) ethylamine.* 10 - Bromodecyldiethylamine (9 g.) in chloroform (10 ml.) was added slowly (40 minutes) to a refluxing solution of 10-diethylaminodecylethylamine (7.9 g.) in chloroform (15 ml.), and the mixture refluxed for a further 30 minutes. On evaporation the residue was basified and extracted with benzene. After removal of solvent, and fractional distillation of the residual oil, *bis - (10 - diethylaminodecyl) ethylamine* was obtained as a pale yellow oil, b.p. 212-216° C./0.25 mm. (3.8 g.)  $n_{D}^{21}$  1.4660.

10 *11:11 - Diethyl - 11 - azoniaheneicosylenebis (triethylammonium) Triiodide.* *Bis - (10 - diethylaminodecyl) ethylamine* (0.93 g.) was refluxed with ethyl iodide (2 ml.) and ethanol (1 ml.) for 50 minutes. Evaporation to dryness under reduced pressure yielded *11:11 - diethyl - 11 - azoniaheneicosylenebis (triethylammonium) triiodide* (1.7 g.), m.p. 204° C. (from acetone-ether). Found: C, 46.1; H, 8.2; N, 4.4; I, 40.5%;  $C_{36}H_{50}N_2I_3$  requires C, 46.2; H, 8.7; N, 4.5; I, 40.7%.

15 **EXAMPLE 6.**

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$$\begin{array}{c} + & + & + \\ | & | & | \\ [Et_3N.(CH_2)_8.S.(CH_2)_8.NEt_3]_3I^- & & \\ | & & \\ Et & & \end{array}$$

*9 - Ethyl - 9 - thoniaheptadecylenebis - (triethylammonium) Triiodide* was prepared from 6 - chlorohexyl - diethylamine through the intermediate *bis - 8 - diethylaminoctyl sulphide* as follows:—

*1:1 - Bisethoxycarbonyl - 7 - diethylaminoheptane* was prepared from 6 - chlorohexyl-diethylamine (44 g.) by the method used in the preparation of *1:1 - bisethoxycarbonyl - 4 - diethylaminobutane* (Edwards, Lewis, Stenlake, and Zona, *J. Pharm. Pharmacol.*, 1957, 9, 1004), with the modification that 10% excess sodium malonic ester was used, and reflux time was increased to 4 hours. *1:1 - Bisethoxycarbonyl - 7 - diethylaminoheptane* was obtained as a pale yellow oil, b.p. 147-155° C./0.8 mm.,  $n_{D}^{15.5}$  1.4472 (34.5 g., 47.65%) and used without characterisation in the next stage of the reaction.

*Ethyl - 8 - diethylaminocaprylate* was prepared from *1:1 - bisethoxycarbonyl - 7 - diethylaminoheptane* (45.2 g.) by the method used for the preparation of *ethyl-5-diethylaminovalerate* (Edwards, Lewis, Stenlake and Zona, *J. Pharm. Pharmacol.*, 1957, 9, 1004), with the modification that the initial reflux time with hydrochloric acid was increased to 4 hours. *Ethyl 8-diethylaminocaprylate* obtained as a colourless oil, b.p. 111-114° C./0.65 mm.,  $n_{D}^{18}$  1.4428 (21.5 g., 62%) was characterised as *7-ethoxycarbonylheptyl triethylammonium iodide* (prepared by the action of ethyl iodide), m.p. 64.5-65.5° C. (from acetone-ether). Found: N, 3.6; I, 32.1 per cent.  $C_{16}H_{34}NO_2I$  requires N, 3.5; I, 32.25 per cent.

*8-Hydroxyoctyldiethylamine.* Ethyl 8-diethylaminocaprylate (35.4 g.) was reduced with lithium aluminium hydride by the method used for the preparation of 5-hydroxypentyldiethylamine (Edwards, Lewis, Stenlake and Zoha, *J. Pharm. Pharmacol.*, 1957, 9, 1004) to yield *8-hydroxyoctyldiethylamine* as a colourless oil b.p. 114-117° C./0.7 mm.,  $n_{D}^{16.5}$  1.5490 (26.2 g., 90%). *Hydrochloride* (from ethanol-ether), m.p. 90-91° C. Found: C, 60.4; H, 11.3; Cl, 15.0 per cent.  $C_{12}H_{22}ONCl$  requires C, 60.6; H, 11.9; Cl, 14.9 per cent.

*8-Chlorooctyldiethylamine* was prepared from *8-hydroxyoctyldiethylamine* (8.6 g.) by the method described for the preparation of 6-chlorohexyldiethylamine (Edwards and Stenlake, *J. Pharm. Pharmacol.*, 1955, 7, 852). *8-chlorooctyldiethylamine* was obtained as a colourless oil, b.p. 94-96° C./0.55 mm.,  $n_{D}^{17}$  1.4550 (9.1 g., 96%). (Altman, *Rec. trav. chim.*, 1938, 57, 941).

*Bis - 8 - diethylaminoctyl sulphide* was prepared from *8-chlorooctyldiethylamine* (9 g.) by the method described for the preparation of *bis - 5 - diethylaminopentyl sulphide*. *Bis - 8 - diethylaminoctyl sulphide* was obtained as a straw-coloured liquid, b.p. 210-212° C./0.65 mm.,  $n_{D}^{16.5}$  1.4768 (5.9 g., 72%). Found: Equiv. (titration) 203.5  $C_{21}H_{42}N_2S$  requires equiv. 200.4. *Dihydrochloride* (from ethanol), m.p. 145° C. Found: C, 60.85; H, 11.0 per cent.  $C_{21}H_{42}N_2SCl_2$  requires C, 60.85; H, 11.5 per cent.

*9 - Ethyl - 9 - thoniaheptadecylenebis - (triethylammonium) triiodide* was prepared from *bis - 8 - diethylaminoctyl sulphide* (0.63 g.) by refluxing with ethyl iodide (4 ml) for 15 minutes. Removal of excess reagent under reduced pressure yielded *9 - ethyl - 9 - thoniaheptadecylenebis - (triethylammonium) triiodide* (0.64 g.) (from ethanol-ether), m.p. 159-160° C. (decomp.). Found: N, 3.2; I, 43.0 per cent.  $C_{36}H_{50}N_2SI_3$  requires N, 3.2; I, 43.8 per cent.

**EXAMPLE 7.**

$$\begin{array}{c} + & + & + \\ | & | & | \\ [Et_3N.(CH_2)_8.N.(CH_2)_8.NEt_3]_3I^- & & \\ | & & \\ Et & & Et \end{array}$$

*9:9 - Diethyl - 9 - azoniaheptadecylenebis - (triethylammonium) Triiodide* was prepared from *8-hydroxyoctyldiethylamine* through the intermediate *8 - bromooctyldiethylamine*, *8 - diethylaminoctylethylamine* and *bis - (8 - diethylaminoctyl) ethylamine* as follows:

*8 - Bromooctyldiethylamine* was prepared from *8 - hydroxyoctyldiethylamine* (8.6 g.) by the method described for *6 - bromohexyldiethylamine*, and was obtained as a golden brown oil (10.3 g., 91.2%)  $n_{D}^{17}$  1.4695, which

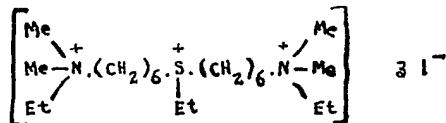
was not further purified.

5      *8 - Diethylaminoocetyl*ethylamine was prepared from 8-bromoocetyl diethylamine (10.3g) by the method described for 10-diethylamino-decylethylamine, and was obtained as a colourless oil, b.p. 104°—106° C./0.7 mm.,  $n_D^{17.5}$  1.4530 (7.4g., 83%). *Dihydrochloride* (from ethanol-ether), m.p. 159.5°—160.5° C. (hygroscopic). Found: N, 9.2; Cl, 23.0 per cent.  $C_11H_{24}N_2Cl_2$  requires N, 9.3; Cl, 23.5 per cent.

10     *Bis - (8 - diethylaminooctyl) ethylamine* was prepared from 8-diethylaminoocetyl ethylamine (6.95g) and 8-chlorooctyl diethylamine (6.7g) by the method described for the preparation of bis - (6 - diethylaminohexyl) ethylamine. *Bis - (8 - diethylaminooctyl) ethylamine* was obtained as a yellow oil, b.p. 230°—250° C. (bath)/0.8 mm.,  $n_D^{17}$  1.4642 (2.3g; 18%). *Trihydrochloride* (from acetone-ether), m.p. 165°—166° C. (decomp.). Found: Cl, 20.9 per cent.  $C_{18}H_{34}N_2Cl_3$  requires Cl, 20.4 per cent.

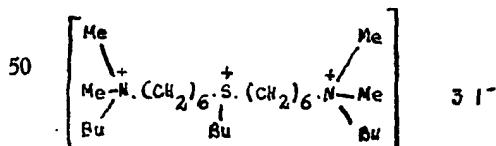
9:9 - *Diethyl - 9 - azoniaheptadecylenebis (triethylammonium) triiodide* was prepared from bis - (8 - diethylaminoctyl) ethylamine (0.56g) by refluxing with ethyl iodide (2 ml) and ethanol (2 ml) for 15 minutes. On evaporation under reduced pressure 9:9 - *diethyl - 9 - azoniaheptadecylenebis (triethylammonium) triiodide* was obtained (from ethanol), m.p. 251-252° C. (decomp.). Found: C, 43.2; H, 8.1; I, 43.0 per cent  $C_{32}H_{72}N_2I_3$  requires C, 43.7; H, 8.25; I, 43.3 per cent.

### EXAMPLE 8.



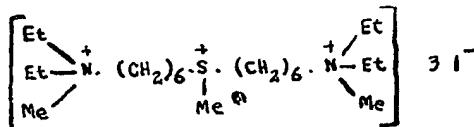
40 7 - Ethyl - 7 - thioniatridecylenebis - (dimethylethylammonium) triiodide was prepared from bis - 6 - dimethylaminohexyl sulphide (0.63g) (Edwards, Lewis, Stenlake and Zoha, *J. Pharm. Pharmacol.*, 1957, 9, 1004) by refluxing with ethyl iodide (2 ml.) and ethanol (2 ml.) for 35 minutes. Evaporation under reduced pressure yielded 7 - ethyl - 7 - thioniatridecylenebis - (dimethylethylammonium) triiodide, (1 g.) m.p. 137-137.5° C. (from ethanol). Found: N, 3.6; I, 50.1%. C<sub>22</sub>H<sub>51</sub>N<sub>2</sub>Si<sub>3</sub> requires N, 3.7; I, 50.3%.

**EXAMPLE 9.**



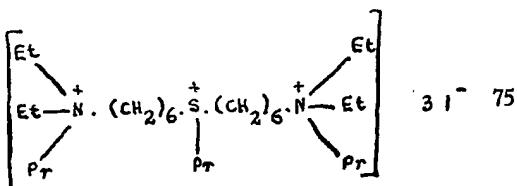
7 - n - Butyl - 7 - thioniatridecylenebis (dimethyl - n - butylammonium) Triiodide was prepared from bis - 6 - dimethylaminohexyl sulphide (0.61 g.) by refluxing with *n*-butyl iodide for 40 minutes. Evaporation under reduced pressure yielded 7 - n - butyl - 7 - thioniatridecylenebis - (dimethyl - n - butylammonium) triiodide (from alcohol-acetone-ether) (0.5 g.) m.p. 151 - 151.5° C. Found: N, 3.4; I, 45.35%  $C_{23}H_{45}N_2Si_3$  requires N, 3.3; I, 45.3%.

**EXAMPLE 10.**



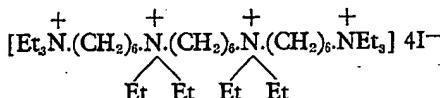
7 - Methyl - 7 - thionatridecylenebis-(diethylmethylammonium) Triiodide was prepared from bis - 6 - diethylamino hexyl sulphide (0.81 g.) by refluxing with methyl iodide (2 ml.) and ethanol (2 ml.) for 20 minutes. Evaporation under reduced pressure yielded 7 - methyl - 7 - thionatridecylenebis - (diethylmethylammonium) triiodide (1.7 g.), m.p. 135-136° C (from ethanol). Found N, 3.6; I, 49.6%.  $C_{22}H_{53}N_2SI_3$  requires N, 3.6; I, 49.4%.

EXAMPLE 11.



7 - n - Propyl - 7 - thioniatridecylenebis - (diethyl - n - propylammonium) Triiodide was prepared from bis - 6 - diethylaminohexyl sulphide (0.78g.) by refluxing with n-propyl iodide (2 ml.) and ethanol (2 ml.) for 45 minutes. Evaporation under reduced pressure yielded 7 - n - propyl - 7 - thioniatridecylenebis - (diethyl - n - propylammonium) triiodide (1.g.), m.p. 125.5 - 126° C (from ethanol-ether). Found: N, 3.3; I, 44.3%.  $C_{22}H_{45}N_2S\bar{I}_3$  requires N, 3.3; I, 44.5%.

EXAMPLE 12.



## METHOD 1.

7:7:14:14 - *Tetraethyl - 7:14 - diazo-niueicosylenebis (triethylammonium) tetraiodide* was prepared from adipoyl chloride and 6 - diethylaminohexyl - ethylamine (Edwards and Stenlake, *J. Pharm. Pharmacol.*, 1955, 7, 852) as follows:—

1:20 - *Bis - (diethylamino) - 7:14 - diethyl-7:14 - diazaeicosane*. Adipic acid (2.54 g.)

5 was refluxed with excess thionyl chloride for 1½ hours. After removal of excess reagent, the acid chloride was heated in benzene (50 ml.) over a water bath, and an excess of 6-diethylaminohexylethylamine (14.2 g.) in benzene (50 ml.) added with stirring (10 minutes). The mixture was then refluxed gently for 10 minutes, cooled and extracted with 10% hydrochloric acid. The latter solution was basified and extracted with benzene. After

15 removal of solvent, the bulk of the 6-diethylaminohexylethylamine was distilled leaving the crude N,N<sup>1</sup> - diethyl - N,N<sup>1</sup> - bis(6 - diethylaminohexyl) - adipamide. Lithium aluminium hydride reduction of this amide in ether, and distillation of the residual oil yielded 1:20 - *bis - (diethylamino) - 7:14 - diethyl - 7:14 - diazaeicosane* as a yellow oil (1.15 g., 13%), n<sub>D</sub><sup>20</sup> 1.4733. B. P. 182° C./0.5 mm. Found: Equiv. (titration) 201.9, C<sub>14</sub>H<sub>30</sub>NO<sub>3</sub> requires equiv. 201.3.

7:7:14:14 - *Tetraethyl - 7:14 - diazo-niueicosylenebis (triethylammonium) tetraiodide*, 1:20 - *Bis - (diethylamino) - 7:14 - diethyl - 7:14 - diazaeicosane* (1.1 g.), ethyl iodide (3 ml.), and ethanol (3 ml.) were refluxed for 20 minutes. Evaporation under

30 reduced pressure and recrystallisation from ethanol yielded 7:7:14:14 - *tetraethyl-7:14 - diazaniaeicosylenebis (triethylammonium) tetraiodide* (1.1 g., 46.2%), m.p. 248.5° —249° C. Found: N, 4.9; I, 45.9 per cent. C<sub>33</sub>H<sub>56</sub>N<sub>2</sub>I<sub>4</sub> requires N, 5.1; I, 45.9 per cent.

## METHOD 2.

7:7:14:14 - *Tetraethyl - 7:14 - diazo-niueicosylenebis (triethylammonium) tetraiodide* was prepared from N,N - diethyladip-

45 amoyl chloride and NN<sup>1</sup> - diethylhexa-

methylenediamine (Wittbecker et al, *J. Amer. Chem. Soc.* 1947, 69, 579) as follows:—

50 N,N - *Diethyladipamic acid*. Ethyl N,N-diethyladipamate (100 g.) was refluxed for 30 minutes with a slight excess (1100 ml.) of N

ethanolic potassium hydroxide (0.8664 —) and

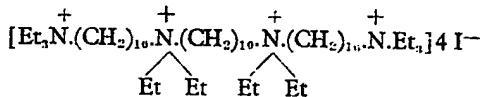
55 the bulk of the ethanol removed by distillation. To the residual liquid was added with stirring hydrochloric acid (50 ml.) and water (50 ml.), and the mixture extracted with benzene, washed with brine and dried (Na<sub>2</sub>SO<sub>4</sub>). After removal of solvent, distillation of the residual oil yielded N,N - *diethyl-adipamic acid* as a yellow viscous oil (83.96 g.; 95.7%), n<sub>D</sub><sup>20</sup> 1.4733. B. P. 182° C./0.5 mm. Found: Equiv. (titration) 201.9, C<sub>14</sub>H<sub>30</sub>NO<sub>3</sub> requires equiv. 201.3.

60 1:20 - *Bis - (diethylamino) - 7:14 - diethyl-7:14 - diazaeicosane*. N,N - *Diethyladipamic acid* (17.4 g.) in benzene (7 ml.) was refluxed with excess thionyl chloride (8 ml.) for 5

minutes. After removal of solvent and excess reagent, the acid chloride in benzene (25 ml.) was added with stirring (25 minutes) to a solution of NN<sup>1</sup> - diethylhexamethylenediamine (7.5 g.) in benzene (40 ml.). The mixture was then refluxed gently for 20 minutes, cooled, extracted with 10% hydrochloric acid, the latter solution basified and extracted with benzene. Removal of solvent yielded crude bis(N - ethyl - N<sup>1</sup>,N<sup>1</sup> - diethyladipamoyl) hexamethylenediamine. Lithium aluminium hydride reduction of this amide and distillation of the residual oil yielded 1:20 - *bis - (diethylamino) - 7:14 - diethyl - 7:14 - diazaeicosane* as a yellow oil (6 g., 28.75%), n<sub>D</sub><sup>22</sup> 1.4665, b.p. 227—229° C./0.6 mm. *Tetrachloride* (from ethanol-ether), m.p. 249—250° C (decomp.) Found: N, 8.98; Cl, 22.3 per cent C<sub>14</sub>H<sub>30</sub>N<sub>2</sub>Cl<sub>4</sub> requires Cl, 22.5 per cent; N 8.9 per cent.

70 7:7:14:14 - *Tetraethyl - 7:14-dazaniaeicosylenebis (triethylammonium) tetraiodide*. As in method 1.

## EXAMPLE 13.



75 11:11:22:22 - *Tetraethyl - 11:22 - diazo-niadotriacetylenebis (triethylammonium) tetraiodide* was prepared from sebacoyl chloride and 10 - diethylaminodecylthylamine as follows:—

100 1:32 - *Bis - (diethylamino) - 11:22 - diethyl - 11:22 - diazadotriacontane* was prepared from sebacic acid (2.53 g.) and 10-diethylaminodecylethylamine (13.1 g.) as described for 1:20 - *bis - (diethylamino) - 7:14 - diethyl - 7:14 - diazaeicosane*, and was obtained as a yellow oil, b.p. 360—380° C

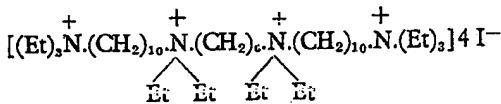
(bath)/0.7 mm. (4.46 g.; 55%) n<sub>D</sub><sup>18</sup> 1.4692, Found: Equiv. (Titration) 165.5 C<sub>42</sub>H<sub>80</sub>N<sub>4</sub> requires equiv. 162.8.

105 11:11:22:22 - *Tetraethyl - 11:22 - diazo-niadotriacetylenebis (triethylammonium) tetraiodide*, 1:32 - *Bis - (diethylamino) - 11:22 - diethyl - 11:22 - diazoniadotriacontane* (0.95 g.) was refluxed with ethyl iodide (3 ml.) and ethanol (3 ml.) for 50 minutes. Evaporation under reduced pressure and recrystallisation from acetone-ether gave 11:11:22:22 - *tetraethyl - 11:22 - diazo-*

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*niadotriacetylenebis (triethylammonium) cent. C<sub>40</sub>H<sub>112</sub>I<sub>4</sub>N<sub>4</sub>* requires C, 47.1; H, 8.7; 5  
*tetraiodide. m.p. 186—187° C (1.4 g.; I, 39.8 per cent.*  
*75.3%) Found: C, 46.8; H, 8.5; I, 39.4 per*

## EXAMPLE 14



11:11:18:18 - *Tetraethyl - 11:18 - diazo-*  
*niacocacylenebis (triethylammonium) Tetra-*  
*iodide was prepared from adipoyl chloride and*  
*10 - diethylaminodecylethylamine as follows:*  
*1:28 - Bis - (diethylamino) - 11:18 - di-*  
*ethyl - 11:18 - diazaoctacosane was prepared*  
*from adipic acid (2.61 g.) and 10-diethyl-*  
*aminodecylethylamine (18.46 g.) as described*  
*for 1:20 - bis - (diethylamino) - 7:14 - di-*  
*ethyl - 7:14 - diazaeicosane, and was obtained*  
*as a yellow oil, b.p. 300—310° C. (bath)/0.6*  
*mm. (6.74 g., 63.4%), n<sub>D</sub><sup>20</sup> 1.4679. Found:*  
*Equiv. 150.2. C<sub>36</sub>H<sub>88</sub>N<sub>4</sub> requires Equiv. 148.8.*  
*Tetrahydrochloride m.p. 161.5—162.5° C*  
*(from ethanol-ether). Found: N, 7.5; Cl 19.2*

per cent. C<sub>36</sub>H<sub>88</sub>N<sub>4</sub>I<sub>4</sub> requires N, 7.6; Cl, 19.15 per cent.

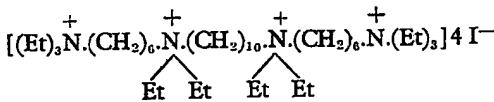
11:11:18:18 - *Tetraethyl - 11:18 - diazo-*  
*niacocacylenebis (triethylammonium) Tetra-*  
*iodide. 1:28 - Bis - (diethylamino) - 11:18 -*  
*diethyl-11:18-diazaoctacosane (0.52 g.) was*  
*refluxed with ethyl iodide (2 ml.) and ethanol*  
*(3 ml.) for 30 minutes. Evaporation under*  
*reduced pressure and recrystallisation from*  
*ethanol yielded 11:11:18:18 - tetraethyl-*  
*11:18 - diazaoctacosylenebis (triethyl-*  
*ammonium) tetraiodide (1.1 g.), m.p. 221—*  
*221.5° C. Found: N, 4.7; I, 41.6 per cent.*  
*C<sub>36</sub>H<sub>102</sub>N<sub>4</sub>I<sub>4</sub> requires N, 4.6; I, 41.6 per cent.*

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## EXAMPLE 15



7:7:18:18 - *Tetraethyl - 7:18 - diazonia-*  
*tetracosylenebis (triethyl - ammonium) Tetra-*  
*iodide was prepared from sebacyl chloride and*  
*6-diethylaminohexylethylamine as follows:—*  
*1:24 - Bis - (diethylamino) - 7:18 - di-*  
*ethyl - 7:18 - diazatetracosane was prepared*  
*from sebamic acid (5.27 g.) and 6-diethylamino-*  
*hexylethylamine (25.4 g.) as described for*  
*(1:20 - bis - (diethylamino) - 7:14 - diethyl-*  
*7:14 - diazaeicosane, and was obtained as a*  
*pale yellow oil, b.p. 280—290° C. (bath)/0.6*  
*mm. (8.15 g., 58%), n<sub>D</sub><sup>20</sup> 1.4673. Found:*  
*Equiv. 135.9. C<sub>34</sub>H<sub>74</sub>N<sub>4</sub> requires Equiv. 134.8.*  
*Tetrahydrochloride, m.p. 196—197° C (from*  
*ethanol-ether). Found: N, 8.1; Cl, 20.3 per*

cent, C<sub>34</sub>H<sub>74</sub>N<sub>4</sub>Cl<sub>4</sub> require N, 8.2; Cl, 20.7 per cent.

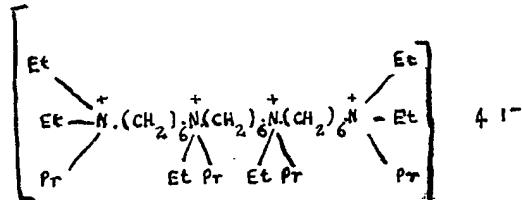
7:18:7:18 - *Tetraethyl - 7:18 - diazonia-*  
*tetracosylenebis (triethylammonium) Tetra-*  
*iodide. 1:24 - Bis - (diethylamino) - 7:18 -*  
*diethyl - 7:18 - diazatetracosane (0.4 g.) was*  
*refluxed with ethyl iodide (2 ml.) and ethanol*  
*(2 ml.) for 30 minutes. Evaporation under*  
*reduced pressure and recrystallisation from*  
*ethanol gave 7:7:18:18 - tetraethyl - 7:18 -*  
*diazoniatetracosylenebis (triethylammonium)*  
*tetraiodide (0.98 g.) m.p. 167.5—168.5° C.*  
*Found: N, 4.7; I, 43.2%. C<sub>42</sub>H<sub>92</sub>N<sub>4</sub>I<sub>4</sub>*  
*requires N, 4.8; I, 43.6%.*

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## EXAMPLE 16

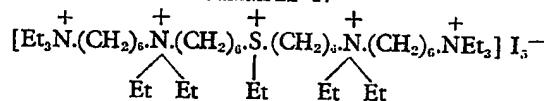


70 7:14 - *Diethyl - 7:14 - di - n - propyl-*  
*7:14 - diazaeicosylenebis (diethyl - n -*  
*propylammonium) Tetraiodide was prepared*  
*from 1:20 - bis - (diethylamino) - 7:14 -*  
*diethyl - 7:14 - diazaeicosane (0.64 g.) by*  
*refluxing with n-propyl iodide (2 ml.) and*  
*ethanol (2 ml.) for 50 minutes. Evaporation*

under reduced pressure yielded 7:14-diethyl-  
*7:14 - di - n - propyl - 7:14 - diazaeicos-*  
*ylenebis (diethyl - n - propylammonium)*  
*tetraiodide (1.4 g.) m.p. 197.5—198.5° C*  
*(decomp.). Found: N, 4.9; I, 43.7 per cent.*  
*C<sub>42</sub>H<sub>92</sub>N<sub>4</sub>I<sub>4</sub> requires N, 4.8; I, 43.6 per cent.*

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## EXAMPLE 17



7:7:14:21:21 - *Pentaethyl - 7:21 - diazonia-14 - thoniaheptacosylenebis (triethylammonium) pentaiodide* was prepared from ethyl hydrogen adipate and 6 - diethylaminoethyl ethylamine as follows:—

5      *Ethyl N - ethyl - N - (6 - diethylamino-hexyl) - adipamate.* Ethyl adipoyl chloride, prepared by refluxing ethyl hydrogen adipate (52 g.) with thionyl chloride in the usual way, was dissolved in benzene (100 ml.) 6 - Diethylaminoethyl ethylamine (58.93 g.) in benzene (25 ml.) was added slowly (45 mins.) with stirring, and the mixture refluxed gently for

10     30 minutes. After extraction with 10% hydrochloric acid, basifying and extraction with ether, fractional distillation yielded *ethyl N-ethyl - N - (6 - diethylaminohexyl) - adipamate* as a yellow oil, b.p. 199—201° C./0.55 mm.,  $n_D^{21.5}$  1.4648 (45.25 g., 43.2%). Found: Equiv. 354.6.  $C_{20}H_{44}N_2O_3$  requires Equiv. 356.5.

25     *13 - Diethylamino - 7 - ethyl - 7 - azatri-decan - 1 - ol.* Ethyl N - ethyl - N - (6 - diethylaminohexyl) - adipamate (35.46 g.) in dry ether (150 ml.) was added to a stirred and refluxing suspension of lithium aluminium hydride (7 g.) in dry ether (600 ml.) at a rate

30     sufficient just to maintain refluxing. The reaction mixture was cooled, and water added dropwise to decompose the excess lithium hydride, and then excess water added. The ethereal layer was decanted and the residue washed with ether. The combined ethereal solutions, were dried ( $Na_2SO_4$ ) evaporated and the residue distilled to yield *13 - diethylamino-7 - ethyl - 7 - azatri-decan - 1 - ol*, as a colourless oil, b.p. 170—175° C./0.55 mm.,  $n_D^{21}$  1.4673 (21 g., 70.3%). Found: Equiv. 149.4.  $C_{11}H_{24}ON_2$  requires Equiv. 150.3. *Dihydrochloride* (from ethanol-ether), m.p. about 155° C. Found: Cl, 19.0 per cent.  $C_{11}H_{22}ON_2Cl_2$  requires Cl, 19.0 per cent.

45     *13 - Diethylamino - 7 - ethyl - 7 - azatri-decyl Chloride* *13 - Diethylamino - 7 - ethyl-7 - azatri-decan - 1 - ol* (19 g.) in benzene (60 ml.) was treated with thionyl chloride (8 ml.)

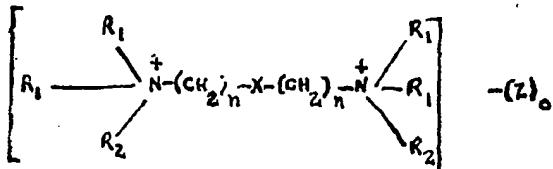
in benzene (20 ml.) The crystalline mass obtained on removal of the solvent and excess reagent was dissolved in water (10 ml.), the solution cooled to 0° and basified with sodium hydroxide solution. Extraction with ether, drying ( $Na_2SO_4$ ), evaporation of the solvent and distillation gave *13 - diethylamino - 7 - ethyl-7 - azatridecyl chloride* as a pale yellow oil, b.p. 167—169° C./0.7 mm.  $n_D^{21}$  1.4648 (13.55 g., 67.1%). Found: Equiv. 158.5.  $C_{16}H_{34}N_2Cl$  requires Equiv. 159.5. *Dihydrochloride* (from ethanol-ether), m.p. 151.5—152.5° C.

50     *Bis - (13 - diethylamino - 7 - ethyl - 7 - azatridecyl) Sulphide* was prepared from 13-diethylamino - 7 - ethyl - 7 - azatridecyl chloride (13.33 g.) and anhydrous sodium sulphide as described for bis - 5 - diethylamino-pentyl sulphide (Edwards, Lewis, Stenlake and Zoha, *J. Pharm. Pharmacol.*, 1957, 9, 1004). *Bis - (13 - diethylamino - 7 - ethyl - 7 - azatridecyl) sulphide* was obtained as a yellow oil, b.p. 305—315° C. (bath)/0.5 mm,  $n_D^{24}$  1.4780, (8.67 g., 69%). Found: Equiv. 150.5.  $C_{16}H_{38}N_4S$  requires 149.8. *Tetrahydrochloride* (from ethanol-ether), m.p. 173—174° C (decomp.). Found: N, 7.5 per cent.  $C_{16}H_{32}N_4SCl_4$  requires N, 7.5 per cent.

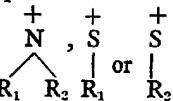
55     *7:7:14:21:21 - Pentaethyl - 7:21 - diazonia-14 - thoniaheptacosylenebis (triethylammonium) pentaiodide.* *Bis - (13 - diethylamino - 7 - ethyl - 7 - azatridecyl) sulphide* (2.1 g.) was refluxed with ethyl iodide (3 ml.) and ethanol (3 ml.) for 35 minutes. Evaporation under reduced pressure and recrystallisation of the product from acetone-ether yielded *7:7:14:21:21 - pentaethyl-7:21 - diazonia - 14 - thoniaheptacosylenebis (triethylammonium) pentaiodide*, m.p. 165.5—166.5° C (decomp.) (3g.; 62%). Found: I, 46.2, N, 4.2 per cent.  $C_{36}H_{103}I_5N_5S$  requires I, 46.0, N, 4.1 per cent.

## WHAT WE CLAIM IS:—

1. A poly-onium compound of the general formula



in which X represents



95     R<sub>1</sub>, R<sub>2</sub> represent alkyl groups and are the same

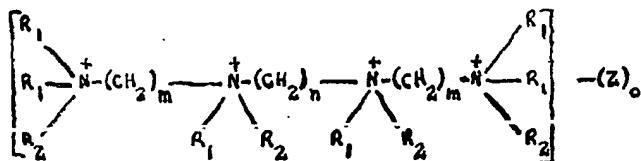
or different

n is an integer not less than 4

Z is a non-toxic anion

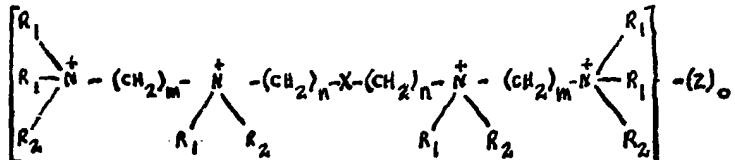
o is equal to the number of onium groups in the compound divided by the valency of the anion.

## 2. A poly-onium of the general formula



in which  $R_1$ ,  $R_2$ ,  $n$ ,  $Z$  and  $o$  are as hereinbefore defined and  $m$  is an integer not less than 4.

## 3. A poly-onium compound of the general formula



in which  $R_1$ ,  $R_2$ ,  $Z$ ,  $X$ ,  $n$ ,  $m$  and  $o$  are as hereinbefore defined.

4. A compound according to any of claims 1 to 3 in which  $R_1$  and  $R_2$  represent alkyl groups containing from 1 to 4 carbon atoms.

5. A compound according to any of claims 1 to 4 in which  $m$  and  $n$  represent integers from 5 to 10.

6. 6 - Ethyl - 6 - thioniaundecylenebis (triethylammonium) triiodide.

7. 7 - Ethyl - 7 - thioniatridecylenebis (triethylammonium) triiodide.

8. 11 - Ethyl - 11 - thioniaheneicosylenebis (triethylammonium) triiodide.

9. 7:7 - Diethyl - 7 - azoniatridecylenebis (triethylammonium) triiodide.

10. 11:11 - Diethyl - 11 - azoniaheneicosylenebis (triethylammonium) triiodide.

11. 9 - Ethyl - 9 - thioniaheptadecylenebis (triethylammonium) triiodide.

12. 9:9 - Diethyl - 9 - azoniaheptadecylenebis (triethylammonium) triiodide.

13. 7 - Ethyl - 7 - thioniatridecylenebis (dimethylethylammonium) triiodide.

14. 7 - n - Butyl - 7 - thioniatridecylenebis (dimethyl - n - butylammonium) triiodide.

15. 7 - Methyl - 7 - thioniatridecylenebis (diethylmethylammonium) triiodide.

16. 7 - n - Propyl - 7 - thioniatridecylenebis - (diethyl - n - propylammonium) triiodide.

17. 7:7:14:14 - Tetraethyl - 7:14-diazoniaeicosylenebis (triethylammonium) tetraiodide.

18. 11:11:22:22 - Tetraethyl - 11:22-diazoniadotriacontylenebis (triethylammonium) tetraiodide.

19. 11:11:18:18 - Tetraethyl - 11:18-diazoniaoctacosylenebis (triethylammonium) tetraiodide.

20. 7:7:18:18 - Tetraethyl - 7:18 - diazoniatetacosylenebis (triethylammonium) tetraiodide.

21. 7:14 - Diethyl - 7:14 - di - n - propyl - 7:14 - diazoniaeicosylenebis (diethyl - n - propylammonium) tetraiodide.

22. 7:7:14:21:21 - Pentaethyl - 7:21-diazonia - 14 - thioniaheptacosylenebis (triethylammonium) pentaiodide.

23. Bis - 5 - diethylaminopentyl sulphide.

24. Bis - (6 - diethylaminohexyl)ethylamine.

25. Bis - (10 - diethylaminodecyl)ethylamine.

26. 1:20 - Bis - (diethylamino) - 7:14-diethyl - 7:14 - diazaeicosane.

27. 1:32 - Bis - (diethylamino) - 11:22-diethyl - 11:22 - diazadotriacontane.

28. Bis - (13 - diethylamino - 7 - ethyl - 7 - azatridecyl) Sulphide.

29. Bis - 8 - diethylaminoctyl sulphide.

30. Bis-(8-diethylaminoctyl) ethylamine.

31. 1:28 - Bis - (diethylamino) - 11:18-diethyl - 11:18 - diazaoctacosane.

32. 1:24 - Bis - (diethylamino) - 7:18-diethyl - 7:18 - diazatetacosane.

33. A method of preparing a poly-onium compound substantially in accordance with any of the Examples.

34. A poly-onium compound prepared by any of the methods of claim 33 or its obvious chemical equivalents.

35. The compound claimed in any of claims 1 to 5, in which the anion is the iodide, or bromide, or chloride, or tartrate.

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## PROVISIONAL SPECIFICATION

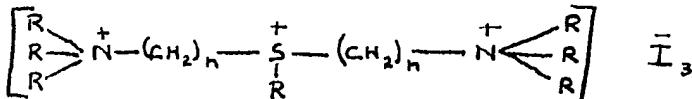
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## Poly-Onium Neuromuscular Blocking Agents

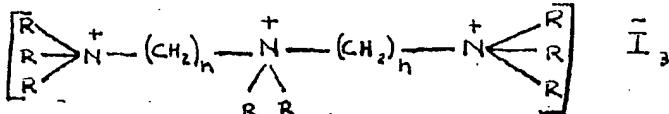
We, NATIONAL RESEARCH DEVELOPMENT CORPORATION, a British Corporation established by Statute, of 1, Tilney Street, London, W.1, do hereby declare this invention to be

5 described in the following statement:—

This invention relates to neuromuscular blocking agents and its object is to provide by synthesis certain tris-onium compounds which



in which R is the ethyl radical ( $\text{Et}=\text{C}_2\text{H}_5$ ) or the methyl radical ( $\text{Me}=\text{CH}_3$ ) and in which n is at least 4.



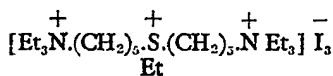
25 in which again R is the ethyl radical or the methyl radical and n is at least 4.

The invention also comprises methods of producing compounds according to the aforesaid general formulae I and II.

30 By way of illustration specific compounds representative of the series according to the foregoing general formulae I and II and methods of preparing such compounds will now be described.

## EXAMPLE 1.

35 This example is according to general formula I in which R is Et in each instance and n is 5. The specific formula is:—



40 This compound, 1:11 - bis - (triethylammonium) - 6 - ethylthiaundecanonium triiodide, was prepared from 5 - hydroxypentyl-diethylamine (according to Synerholm, *Journal American Chemical Society*, 1947, 69 2581) through the intermediate bis - 5 - diethylaminopentyl sulphide as follows:—

45 *Bis-5-diethylaminopentyl Sulphide.* Excess thionyl chloride (9 ml.) in benzene (20 ml.) was slowly added to a stirred solution of 5 - hydroxypentyl-diethylamine (14.3 g.) in benzene (100 ml.). The yellow crystalline mass obtained on removal of the solvent and excess reagent was dissolved in water (20 ml.); the solution was cooled to 0° C and basified with sodium hydroxide solution (30 ml.; 20%).

55 Extraction with ether, drying ( $\text{Na}_2\text{SO}_4$ ) and

have been found to have properties by virtue of which they are suitable as such agents, acting in some respects like (+)-tubocurarine and decamethonium.

The invention comprises the tris-onium compounds symbolized by the general formula (I):—

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20 The invention also comprises the tris-onium compounds symbolized by the general formula (II):—

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55 evaporation of the solvent gave crude 5-chloropentyl-diethylamine (15.9 g.). The latter in ethanol (8 ml.) was slowly added to a hot solution of anhydrous sodium sulphide (4.4 g.) in water (5 ml.) and ethanol (16 ml.), and the mixture was refluxed for 3 hours with continuous stirring. The residual liquid, after removal of the solvent at 100° was poured into brine (50 ml.) and extracted with ether. The ethereal extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated, and the residue was distilled, yielding *bis - 5 - diethylaminopentyl sulphide* as a pale yellow oil (3.55 g., 25%), b.pt. 200—205° C/1.2 mm. 1:11 - (triethylammonium) - 6 - ethylthiaundecanonium Triiodide. Bis - 5 - diethylaminopentyl sulphide (0.85 g.) was refluxed with excess ethyl iodide (4 ml.) for not less than 40 minutes. Removal of excess reagent under reduced pressure and recrystallisation of the product from ethanol gave 1:11 - bis(triethylammonium) - 6 - ethylthiaundecanonium triiodide, m.pt. 136.5—137.5° C.

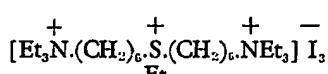
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80 EXAMPLE 2. This example also is according to general formula I in which R again is Et in each instance and n is 6. The specific formula is:—



85 This compound, 1:13 - bis - (triethylammonium) - 7 - ethylthiatridecanonium triiodide, was prepared from bis - 6 - diethylaminohexyl

5 sulphide (according to Edwards and Stenlake, *Journal of Pharmacy and Pharmacology*, 1955, 7, 852) (1.64 g.) by refluxing with ethyl iodide (3 ml.) for 25 mins. Removal of excess reagent under reduced pressure and recrystallisation of the product from ethanol gave almost colourless crystals of *1:13 - bis - (triethylammonium) - 7 - ethylthiazatridecanonium triiodide* (2.95 g., 76.3%) m.pt. 142—143° C.

10 **EXAMPLE 3.**  
This example also is according to general formula I in which R again is Et in each instance and n is 10. The specific formula is:—

15 
$$[Et_3N.(CH_2)_{10}S.(CH_2)_{10}.NEt_3] I_3$$

20 This compound *1:21 - bis(triethylammonium)-11-ethylthiazaheneicosonium triiodide*, was prepared from bis - 10 - diethylaminodecyl sulphide (1.1 g.) (according to Edwards and Stenlake, *Journal of Pharmacy and Pharmacology*, 1955, 7, 852) by refluxing with ethyl iodide (2 ml.) and ethanol (1 ml.) for 45 minutes. Evaporation to dryness under reduced pressure yielded *1:21 bis (triethylammonium) - 11 - ethylthiazaheneicosonium triiodide* (0.6 g.) m.p. 123.5—124° C (from acetone-ether).

25 **EXAMPLE 4.**  
This example is according to general formula II in which R is Et in each instance and n is 6. The specific formula is:—

30 
$$[Et_3N.(CH_2)_6N.(CH_2)_6.NEt_3] I_3$$

35 This compound, *1:13 - bis(triethylammonium) - 7 - diethylazatridecanonium triiodide*, was prepared from 6 - hydroxyhexyldiethylamine (according to Work, *Journal of the Chemical Society*, 1942, 426; and Edwards and Stenlake, *Journal of Pharmacy and Pharmacology*, 1955, 7, 852) through the intermediate 6-bromo hexyldiethylamine, 6-diethylaminohexyldiethylamine and bis (6-diethylaminohexyl) ethylamine as follows:—

40 *6 - Bromohexyldiethylamine.* 6 - Hydroxyhexyldiethylamine (19 g.) was refluxed with 48% hydrobromic acid (63 ml.) and concentrated sulphuric acid (8.7 ml.) for 5 hours. The cooled solution, diluted with water (50 ml) was basified with sodium carbonate, and extracted with chloroform. Evaporation of the solvent under reduced pressure at 17° C, and filtration of solid matter from the oily residue gave 6 - bromohexyldiethylamine (15.1 g.) as a reddish brown oil, which was used immediately in the next stage.

45 *6 - Diethylaminohexyldiethylamine Hydrochloride.* Crude 6-bromo hexyldiethylamine (15 g.) in chloroform (50 ml.) and excess ethylamine (20 ml.) were refluxed for 1 hour. Evaporation of the chloroform and excess ethylamine, addition of water to the residue and extraction with benzene yielded an oily product which on distillation gave crude 6-diethylaminohexyldiethylamine (5.4 g.) b.p. 125° C/16 mm. Treatment of the product with dilute hydrochloric acid and evaporation to dryness gave *6 - diethylaminohexyldiethylamine dihydrochloride*, m.p. 172—173° C (from ethanol-ether).

50 *Bis - (6 - diethylaminohexyl) ethylamine.* Crude 6 - diethylaminohexyldiethylamine (3.55 g.) was refluxed with 6 - bromohexyldiethylamine (2.2 g.) in chloroform (40 ml.) for  $\frac{3}{4}$  hour, allowed to stand overnight, and the solution evaporated to dryness under reduced pressure. Addition of water to the residue, extraction with benzene, evaporation of the solvent and fractional distillation of the residue gave *bis - (6 - diethylaminohexyl) - ethylamine*, as an oil (0.43 g.) b.p. 152—153° C/0.4 mm.

55 *1:13 - Bis - (triethylammonium) - 7 - diethylazatridecanonium triiodide.* Bis - (6 - diethylaminohexyl)ethylamine (0.39 g.) was refluxed with ethyl iodide (3 ml.) for 15 minutes. Evaporation of excess ethyl iodide yielded *1:13 - bis(triethylammonium) - 7 - diethylazatridecanonium triiodide* (0.57 g.) m.p. 247—248° C (from ethanol).

60 **EXAMPLE 5.**  
This example also is according to general formula II in which R again is Et in each instance and n is 10. The specific formula is:—

65 
$$[Et_3N.(CH_2)_{10}N.(CH_2)_{10}.NEt_3] I_3$$

70 This compound, *1:21 - bis(triethylammonium) - 11 - diethylazaheneicosonium triiodide*, was prepared from 10 - hydroxydecyl-diethylamine (according to Schinzel and Benoit, *Bulletin Société Chemie Française*, 1939, 6, 501; and Edwards and Stenlake, *Journal of Pharmacy Pharmacology*, 1955, 7, 852) through the intermediate 10 - bromodecyldiethylamine, 10 - diethylaminodecyl-diethylamine and bis (10 - diethylaminodecyl) ethylamine as follows:—

75 *10 - Bromodecyldiethylamine.* This intermediate compound was prepared from 10-hydroxydecyl-diethylamine (20.1 g.) by the method described in Example 4 for preparing 6 - bromohexyldiethylamine and was obtained as a colourless oil (21.4 g.) b.p. 130—131° C/0.65 mm.

80 *10 - Diethylaminodecylethylamine.* 10-Bromodecyldiethylamine (20.9 g.) and excess

85 *10 - Diethylaminodecylethylamine.* 10-Bromodecyldiethylamine (20.9 g.) and excess

90 *10 - Diethylaminodecylethylamine.* 10-Bromodecyldiethylamine (20.9 g.) and excess

95 *10 - Diethylaminodecylethylamine.* 10-Bromodecyldiethylamine (20.9 g.) and excess

100 *10 - Diethylaminodecylethylamine.* 10-Bromodecyldiethylamine (20.9 g.) and excess

105 *10 - Diethylaminodecylethylamine.* 10-Bromodecyldiethylamine (20.9 g.) and excess

110 *10 - Diethylaminodecylethylamine.* 10-Bromodecyldiethylamine (20.9 g.) and excess

ethylamine (60 ml.) were refluxed for 2 hours. Distillation of the excess ethylamine, addition of water to the residue and extraction with benzene yielded an oily product which on distillation gave 10 - diethylaminodecylethylamine (14 g.) b.p. 133-135° C/0.8 mm. together with bis - (10 - diethylaminodecyl)-ethylamine (0.9 g.) b.p. 216-217° C/0.75 mm.

10 Bis - (10 - diethylaminodecyl)-ethylamine. This intermediate compound was prepared from 10 - diethylaminodecylethylamine (7.9 g.) and 10 - bromodecylidethylamine (9 g.) as described in Example 4 for preparing bis(6-diethylaminohexyl)-ethylamine and was obtained as a pale yellow oil (3.6 g.) b.p. 216-217° C/0.75 mm.

15 1:21 - Bis(triethylammonium) - 11 - diethylazaheneicosanonium triiodide. Bis (10 - diethylaminodecyl)-ethylamine (0.93 g.) was refluxed with ethyl iodide (2 ml.) and ethanol (1 ml.) for 50 minutes. Evaporation to dryness under reduced pressure yielded 1:21-bis (triethylammonium) - 11 - diethylazaheneicosanonium triiodide (1.7 g.), m.pt. 204° C (from acetone-ether).

20 In the foregoing, although iodine has been specified throughout as the anion, this element as such is not critical to the activity of each compound as a blocking agent, and therefore there may be substituted any pharmaceutically equivalent anion, for example the bromide, the chloride, or the tartrate.

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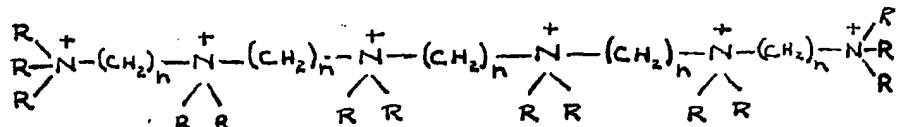
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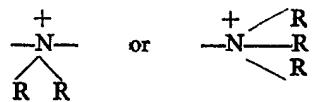
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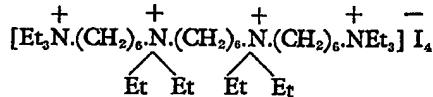
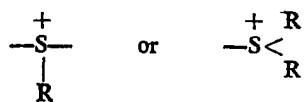
The hexa-quaternary component of the compounds may be symbolized by the general formula (IV):—



5 In the compounds above depicted, each quaternary component is a quaternary nitrogen group, namely:—



10 There may be incorporated instead of any one or more of these groups the equivalent tertiary sulphur group, namely:—



30 This compound, 7:7:14:14 - *Tetraethyl-7:14 - diazaeicoslenebis (triethylammonium) tetraiodide* was prepared from 6-hydroxyhexyldiethylamine (according to Work, *Journal of the Chemical Society*, 1942, 426; and Edwards and Stenlake, *Journal of Pharmacy and Pharmacology*, 1955, 7, 852) as follows:—

35 6 - *Bromohexyldiethylamine*. 6 - Hydroxyhexyldiethylamine (19 g.) was refluxed with 48% hydrobromic acid (63 ml.) and concentrated sulphuric acid (8.7 ml.) for 5 hours. The cooled solution, diluted with water (50 ml.) was basified with sodium carbonate, and extracted with chloroform. Evaporation of the solvent under reduced pressure at 17° C and filtration of solid matter from the oily residue gave 6 - bromohexyldiethylamine (15.1 g.) as a reddish brown oil, which was used immediately in the next stage.

40 6 - *Diethylaminohexylethylamine*. Crude 6-bromohexyldiethylamine (15 g.) in chloroform (50 ml.) and excess ethylamine (20 ml.) were refluxed for 1 hour. Evaporation of the chloroform and excess ethylamine, addition of water to the residue and extraction with benzene yielded an oily product which on distillation gave crude 6-diethylaminohexylethylamine (5.4 g.) b.p. 125° C/16 mm.

45 1:20 - *Bis (diethylamino) 7:14 - diethyl-7:14 - diazaeicosane* Adipic acid (2.54 g.) was refluxed with excess thionyl chloride for 1½ hours. After removal of excess reagent, the

The invention also comprises methods of producing compounds according to the aforesaid general formulae I to IV, each quaternary group being a nitrogen or equivalent sulphur group. 15

By way of illustration specific compounds representative of the series according to the foregoing general formulae and methods of preparing such compounds will now be described. 20

#### EXAMPLE 1.

This example is according to general formula II in which in each instance R is Et and n is 6. The specific formula is:—

25

acid chloride was heated in benzene (50 ml.) over a water bath, and an excess of 6-diethylaminohexylethylamine (14.2 g.) in benzene (50 ml.) added with stirring (10 minutes). The mixture was then refluxed gently for 10 minutes, cooled and extracted with 10% hydrochloric acid. The latter solution was basified and extracted with benzene. After removal of solvent, the bulk of the 6-diethylaminohexylethylamine was distilled leaving the crude N,N<sup>1</sup> - diethyl - N,N<sup>1</sup> - bis(6 - diethylaminohexyl) - adipamide. Lithium aluminium hydride reduction of this amide in ether, and distillation of the residual oil yielded 1:20 - *bis - (diethylamino) - 7:14 - diethyl - 7:14 - diazaeicosane* as a yellow oil (1.15 g., 13%),  $n_{D}^{20}$  1.4695, b.p. 178-185° C./0.25 mm. 60

7:7:14:14 - *Tetraethyl - 7:14 - diazaeicoslenebis (triethylammonium) tetraiodide*. 1:20 - *Bis - (diethylamino) - 7:14 - diethyl - 7:14 - diazaeicosane* (1.1 g.), ethyl iodide (3 ml.), and ethanol (3 ml.) were refluxed for 20 minutes. Evaporation under reduced pressure and recrystallisation from ethanol yielded 7:7:14:14 - *tetraethyl-7:14 - diazaeicoslenebis (triethylammonium) tetraiodide* (1.1 g., 46.2%), m.p. 239.5-240° C. Found: N, 4.9; I, 45.9 per cent.  $C_{38}H_{86}N_4I_4$  requires N, 5.1; I, 45.9 per cent. 65

#### EXAMPLE 2.

This example also is according to general formula II in which in each instance R again is Et but n is 10. The specific formula is:—

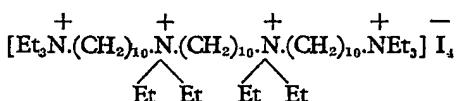
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11:11:22:22 - *Tetraethyl - 11:22 - diazo-niadotriacetylenebis (triethylammonium) tetraiodide* was prepared from sebacyl chloride and 10-diethylaminodecylethylamine as follows:—

1:32 - *Bis - (diethylamino) - 11:22 - diethyl - 11:22 - diazadotriaccontane* was prepared from sebacic acid (2.53 g.) and 10-diethylaminodecylethylamine (13.1 g.) as described for 1:20 - *bis - (diethylamino) - 7:14 - diethyl - 7:14 - diazaeicosane*, and was obtained as a yellow oil, b.p. 360—380° (bath) 0.7 mm. (4.46 g.; 55%  $n_D^{18}$  1.4692 Found: 15 Equiv. (Titration) 165.5  $C_{42}H_{90}N_4$  requires equiv. 162.8.

11:11:22:22 - *Tetraethyl - 11:22 - diazo-niadotriacetylenebis (triethylammonium)*

11:11:22:22 - *Tetraethyl - 11:22 - diazo-niadotriacetylenebis (triethylammonium) tetraiodide*. 1:32 - *Bis - (diethylamino) - 11:22 - diethyl - 11:22 - diazadotriaccontane* (0.95 g.) was refluxed with ethyl iodide (3 ml.) and ethanol (3 ml.) for 50 minutes. Evaporation under reduced pressure and recrystallisation from acetone-ether gave 11:11:22:22 - *tetraethyl - 11:22 - diazo-niadotriacetylenebis (triethylammonium) tetraiodide*, m.p. 186—187° (1.4 g.; 75.3%) Found: C, 46.8; H, 8.5; I, 39.4 per cent.  $C_{50}H_{110}I_4N_4$  requires C, 47.1; H, 8.7; I, 39.8 per cent. 20

15 Equiv. (Titration) 165.5  $C_{42}H_{90}N_4$  requires equiv. 162.8. 25

11:11:22:22 - *Tetraethyl - 11:22 - diazo-niadotriacetylenebis (triethylammonium)*

11:11:22:22 - *Tetraethyl - 11:22 - diazo-niadotriacetylenebis (triethylammonium) pentaiodide* was prepared from ethyl hydrogen adipate and 6-diethylamino-hexylethylamine as follows:—

13 - *Diethylamino - 7 - ethyl - 7 - azatri-decyl Chloride*. 13 - *Diethylamino - 7 - ethyl - 7 - azatri-decan - 1 - ol* (7.53 g.) in benzene (20 ml.) was treated with thionyl chloride (5 ml.) in benzene (10 ml.). The crystalline mass obtained on removal of the solvent and excess reagent was dissolved in water (10 ml.), the solution cooled to 0° and basified with sodium hydroxide solution. Extraction with ether, drying ( $Na_2SO_4$ ), evaporation of the solvent and distillation gave 13 - *diethylamino - 7 - ethyl - 7 - azatri-decyl chloride* as a pale yellow oil, b.p. 140—148°/0.2 mm.  $n_D^{17}$  1.4670 (5.7 g.; 71%). 75

13 - *Diethylamino - 7 - ethyl - 7 - azatri-decyl Sulphide* was prepared from 13-diethylamino - 7 - ethyl - 7 - azatri-decyl chloride (5.65 g.) and anhydrous sodium sulphide as described for bis - 5 - diethylamino-pentyl sulphide (according to Edwards, Lewis, Stenlake, Zoha; *Journal of Pharmacy and Pharmacology*, 1957, Vol. 9, page 1004). *Bis - (13 - diethylamino - 7 - ethyl - 7 - azatri-decyl) sulphide* was obtained as a pale yellow oil, b.p. 300—310° (bath)/0.33 mm.,  $n_D^{12.5}$  1.4855, (1.38 g.; 26%). 90

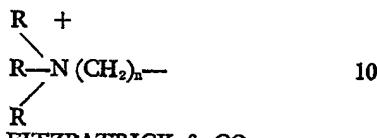
7:7:14:21:21 - *Pentaethyl - 7:21 - diazonia - 14 - thioniaheptacosylenebis (triethylammonium) pentaiodide*. Bis - (13 - diethylamino - 7 - ethyl - 7 - azatri-decyl) sulphide (0.24 g.) was refluxed with ethyl iodide (1 ml.) and ethanol (2 ml.) for 20 minutes. Evaporation under reduced pressure and re-crystallisation of the product from acetone-ether yielded 7:7:14:21:21 - *pentaethyl - 7:21 - diazonia - 14 - thioniaheptacosylenebis (triethylammonium) pentaiodide*, m.p. 100

7:7:14:21:21 - *Pentaethyl - 7:21 - diazonia - 14 - thioniaheptacosylenebis (triethylammonium) pentaiodide*. Bis - (13 - diethylamino - 7 - ethyl - 7 - azatri-decyl) sulphide (0.24 g.) was refluxed with ethyl iodide (1 ml.) and ethanol (2 ml.) for 20 minutes. Evaporation under reduced pressure and re-crystallisation of the product from acetone-ether yielded 7:7:14:21:21 - *pentaethyl - 7:21 - diazonia - 14 - thioniaheptacosylenebis (triethylammonium) pentaiodide*, m.p. 105

7:7:14:21:21 - *Pentaethyl - 7:21 - diazonia - 14 - thioniaheptacosylenebis (triethylammonium) pentaiodide*. Bis - (13 - diethylamino - 7 - ethyl - 7 - azatri-decyl) sulphide (0.24 g.) was refluxed with ethyl iodide (1 ml.) and ethanol (2 ml.) for 20 minutes. Evaporation under reduced pressure and re-crystallisation of the product from acetone-ether yielded 7:7:14:21:21 - *pentaethyl - 7:21 - diazonia - 14 - thioniaheptacosylenebis (triethylammonium) pentaiodide*, m.p. 105

149—150° (decomp.) (0.12 g.; 22%) Found: I, 46.2 per cent.  $C_{46}H_{103}I_5N_4S$  requires I, 46.0 per cent.

5 In the foregoing specification the poly-quaternary compounds as symbolized by the formulae I, II, III and IV, R is stated to represent an alkyl radical. Instead, in any one or more instances, R may be an  $\omega$ -trialkyl-ammoniumalkyl group, namely:—



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